Application of Cross-Coupling and Metalation Chemistry of 3(2*H*)-Pyridazinones to Fungicide and Herbicide Discovery

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Dedicated to the memory of Michael P. Walker

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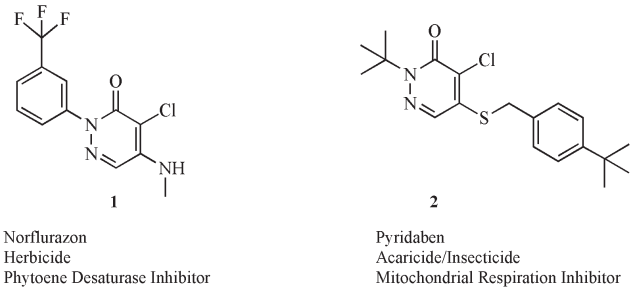
Introduction.

Pyridazinones have played an important role in the chemistry of crop protection products. The nucleophilic displacement chemistry of 4,5-dihalo-3-(2*H*)-pyridazinones has long been exploited for the synthesis of both commercially important herbicides and insecticides. Two examples are shown in Figure 1. It follows that the pyridazinone nucleus confers biological and physical properties to molecules that are favorable for their development as crop protection agents. Therefore, we wished to extend halopyridazinone chemistry from nucleophilic displacement to metal mediated processes for C-C bond formation in hopes of discovering new classes of biologically active pyridazines.



1

Norflurazon
Herbicide
Phytoene Desaturase Inhibitor

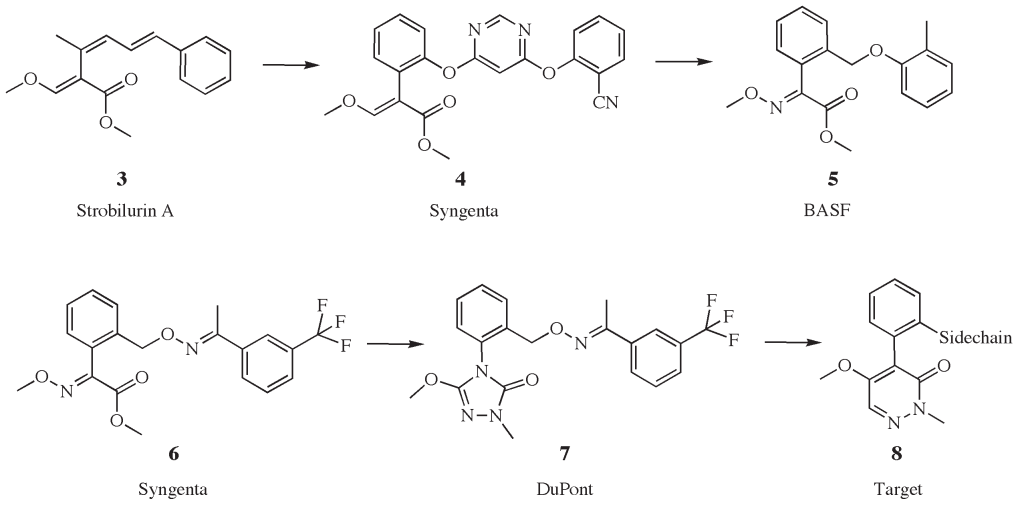
2

Pyridaben
Acaricide/Insecticide
Mitochondrial Respiration Inhibitor

Figure 1. Some Commercial Pyridazinone Containing Crop Protection Products

Strobilurin Fungicides.

The isolation and structural determination of the fungicidal natural product Strobilurin A (**3**) from the basidiomycete fungus *Strobilurus tenacellus* was the starting point for fruitful research programs at many companies, which have subsequently led to commercialization of several successful agricultural fungicides. [1] The site of action of this compound was shown to be inhibition of mitochodrial respiration at the cytochrome bc_1 complex. [2] The unique and simple β-methoxyacrylate containing structure proved to be readily amenable to modification with retention of activity. The natural product was unfortunately very photolabile and therefore not very effective in testing on whole plants in direct sunlight. A solution to the photostability problem was soon arrived at as scientists from both ICI (now Syngenta) and BASF simply replaced the double bond *proximal* to the β-methoxyacrylate with an aromatic ring as in **4**. Further modification of the molecule in both the pharmacophore and side chain led eventually to



3
Strobilurin A

4
Syngenta

5
BASF

6
Syngenta

7
DuPont

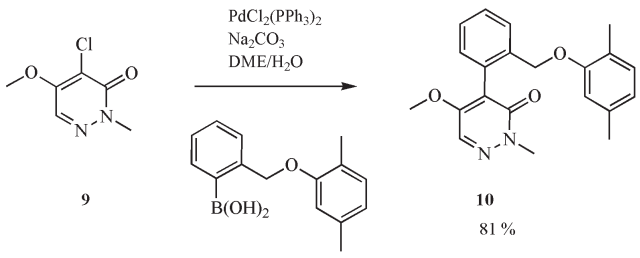
8
Target

Figure 2. Evolution of Strobilurin Analogs

a number of commercial products such as Syngenta's trifloxystrobin (**6**), which contains an oxime containing pharmacophore and an acetophenone oxime containing side chain. (Figure 2) The successful modification of the natural methoxyacrylate pharmacophore inspired scientists at DuPont to investigate N-methyltriazolinones (**7**) as cyclic pharmacophores, which proved to be highly active fungicides. [3] In light of these last pharmacophores, replacing the triazolinone ring with an appropriately substituted pyridazinone became an appealing synthetic target.

Synthesis of the target pyridazinone was envisioned to proceed via a Suzuki coupling of a 5-methoxy-4-halopyridazinone (**9**). At the ouset of this work in 1994 no transition metal catalyzed reactions were yet known for the pyridazinone ring system. [4] Our initial work began with a simple reaction of a commercially available chloropyridazinone (**9**) with phenyl boronic acid. The coupling carried out with tetrakis-(triphenylphosphino)palladium gave a good yield of N-methyl-5-methoxy-4-phenyl-3(2*H*)-pyridazinone with standard Suzuki coupling conditions. It turned out that inexpensive bis(triphenylphosphino) palladium dichloride was almost as efficient in promoting the cross-coupling. Coupling with a boronic acid already substituted with a typical strobilurin side chain provided the first target molecule (**10**), which proved to be an active fungicide as well as an inhibitor of mitochondrial respiration. (Scheme 1) We then sought a more convergent approach for analoging.

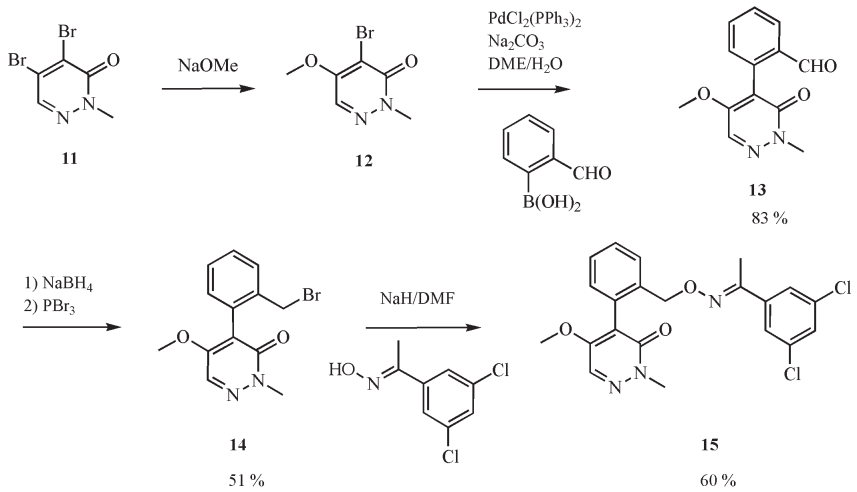
Scheme 1



Synthesis of a Pyridazinone Strobilurin Analog

In order to get compounds with more diverse sidechains we used commercially available 2-formylbenzene boronic acid to make a common intermediate. (Scheme 2) We also turned to the use of the 4-bromopyridazinone (**12**) as a more reactive coupling partner since 2-formylphenyl boronic acid has been reported to be prone to deboronation. [5] Reduction of the Suzuki product (**13**) with either lithium borohydride or more conveniently sodium borohydride gave the corresponding alcohol in good yield. Bromination provided a key benzylic bromide (**14**) that could be used to introduce oximes of acetophenone as side chains. While a number of different methods could be used for halogenation of the alcohol, PBr_3 in ether at room temperature was most successful. Interestingly, an alternate synthesis via benzylic bromination of a 4-(o-tolyl)pyridazinone was not efficient. The reaction of the bromide with oximes of various substituted acetophenones was efficient and could be carried out with sodium hydride or potassium carbonate as base to give **15** and related analogs. The compounds with oxime side chains proved to be very good fungicides. Highest levels of activity were observed for compounds with 3,5-disubstitution. Optimal activity for plant protection was seen for the 3,5-dichloroacetophenone oxime (**15**), which provided

Scheme 2



Analoging Scheme for Strobilurin Analogs

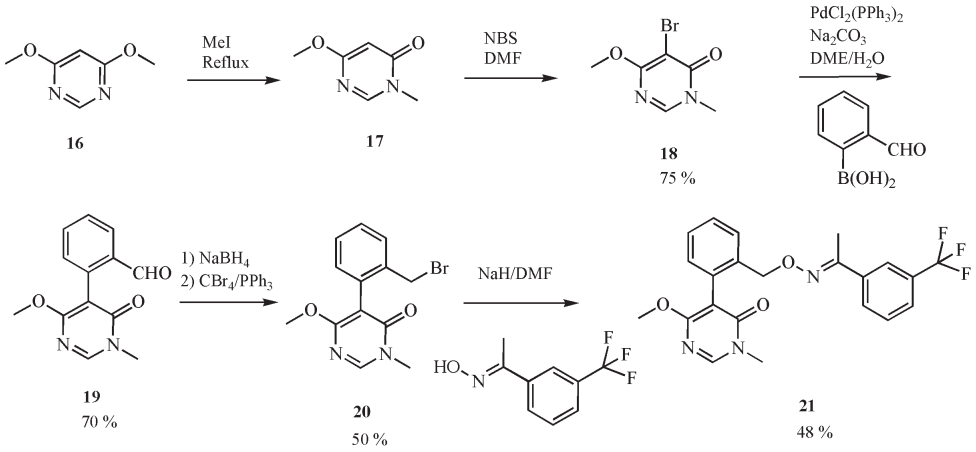
broad-spectrum control of important plant pathogens at 40 ppm. Optimal activity at the site of action (inhibition of mitochondrial respiration at the cytochrome bc_1 site) was found for product from 3,5-bis(trimethylsilyl)acetophenone oxime which exhibited low nanomolar inhibition.

We also extended the chemistry to other heterocyclic ring systems. Most notably pyrimidinones proved to be very good surrogates for the pyridazinone system. (Scheme 3) The first step in the process was the synthesis of the appropriately substituted pyrimidinone (**17**) by an interesting N-methylation of the 4,6-dimethoxypyrimidine (**16**). [6] The pyrimidinone (**17**) was brominated at the 5-position with NBS to give the Suzuki intermediate alcohol gave the benzylic bromide (**20**), which was coupled with acetophenone oximes to give the desired products such as **21**. The fungicidal activity and mitochondrial respiration activity of the pyrimidinones was good. However, the pyridazinone ring system proved to be slightly more active as a strobilurin pharmacophore replacement. However, neither of the 6-membered pharmacophores were as effective as the triazolinone pharmacophore found in **7** in fungicidal testing.

Herbicidal Suzuki Coupling Products.

The success of the Strobilurin chemistry led us to investigate a broader range of 4-bromo, 5-methoxy substituted

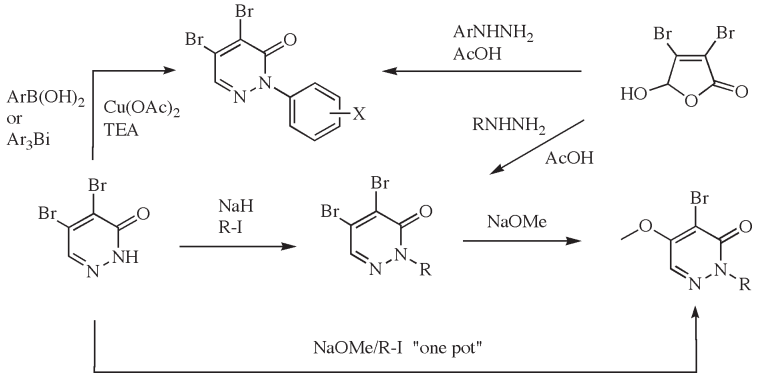
Scheme 3



Pyrimdinone Strobilurin Pharmacophore Synthesis

reaction substrate (**18**). Suzuki reaction of **18** with 2-formylphenylboronic acid gave the expected 5-arylpyrimidinone (**19**) in good yield. Reduction with sodium borohydride followed by bromination of the pyridazinones in Suzuki couplings. (Scheme 4) Many substrates were prepared by traditional methods via reaction of mucobromic acid with various aryl or alkyl hydrazines followed by reaction with sodium methoxide. [7]

Scheme 4



Synthetic Methods for Starting Materials

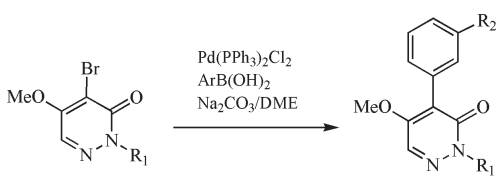
Selectivity for the methoxide displacement generally was at least 15:1 in favor of the 5-methoxy product over the 4-methoxy product when the reaction was carried out in methanol as solvent. We were easily able to prepare a variety of N-alkyl pyridazinones by alkylation of commercially available 4,5-dibromopyridazinone. The alkyl groups and the methoxy group could be appended in a single step by reaction of alkyl bromides or iodides using sodium methoxide as both base and nucleophile. [8] Arylation of the 4,5-dibromopyridazinone was achieved by copper mediated reaction with triarylbismuth reagents in the presence of triethylamine. [9] Arylation was also possible by a related process using commercially available boronic acids in place of the triarylbismuth reagents. [10]

We broadly investigated coupling of these pyridazinone substrates with a variety of different commercially available phenyl boronic acids. Two active classes of herbicidal pyridazinones emerged from the Suzuki coupling products. We found interesting bleaching herbicide activity for compounds **22-27** derived from coupling with 3-trifluoromethylphenyl boronic acid and 3-trifluoromethoxyphenyl boronic acid. (Table 1) Highest activity was found for the N-aryl compounds (**22**) and (**23**). The most active analogs controlled a variety of important weeds at 400-1000 g/Ha. The site of action for these compounds was determined to be inhibition of phytoene desaturase, which is a key step in the biosynthesis of carotenoids in plants. Relative pre-emergent herbicidal activity in greenhouse testing for the compounds in Table 1 at 1000 g/Ha was **22** > **23** > **24** > **25** >> **26**, **27**.

A second class of herbicidal compounds was derived from *o*-tolyl boronic acid. (Scheme 5) We had synthesized a sizable quantity of the N-methylpyridazinone Suzuki adduct (**28**) as a potential intermediate for Strobilurin analog synthesis, but poor yields were obtained in radical bromination. Because of the resemblance of the *o*-tolyl products to herbicidal acetyl coA carboxylase (ACCase) inhibitors from Syngenta and Bayer [11], we carried out demethylation of **28** to the hydroxypyridazinone (**29**) with boron tribromide in dichloromethane. To change the physical properties of the compound, we esterified the free hydroxy group with pivaloyl chloride to give **30**. Both **29** and **30** showed good pre-emergent herbicidal activity on grass weeds at 1000 g/Ha, as well as symptomology consistent with the herbicidal effects of ACCase inhibitors. [11] Repeating the synthetic sequence with pyridazinones bearing larger N-substituents (phenyl, benzyl and *t*-butyl) was equally successful, but only the N-methyl products showed good levels of herbicide activity.

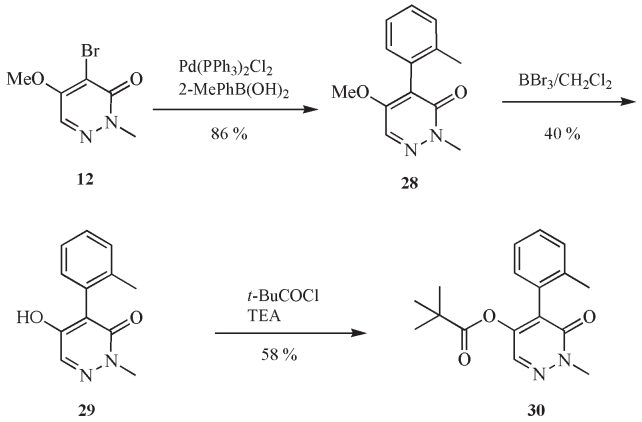
Table 1

Herbicidal 4-Arylpyridazinones



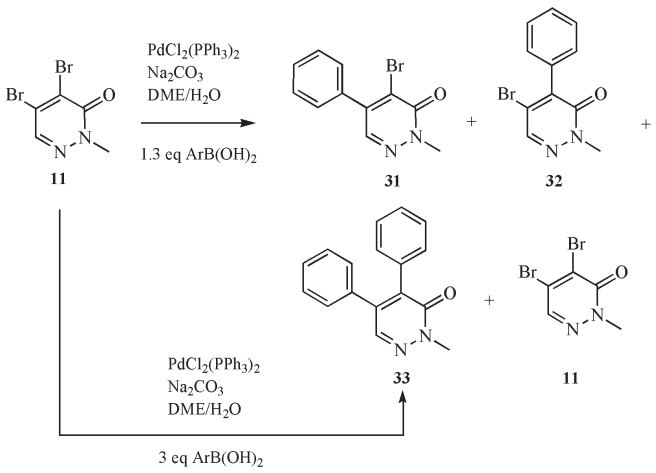
R_1	R_2	Reaction Product	Yield (%)
3-F-Ph	3-CF_3	**22**	83
3-CF_3-Ph	3-OCF_3	**23**	46
Ph	3-CF_3	**24**	80
Me	3-CF_3	**25**	88
4-CF_3-Ph	3-CF_3	**26**	92
t-Bu	3-CF_3	**27**	72

Scheme 5



Herbicidal Suzuki Coupling Products from *o*-Tolyl Boronic Acid

Scheme 6



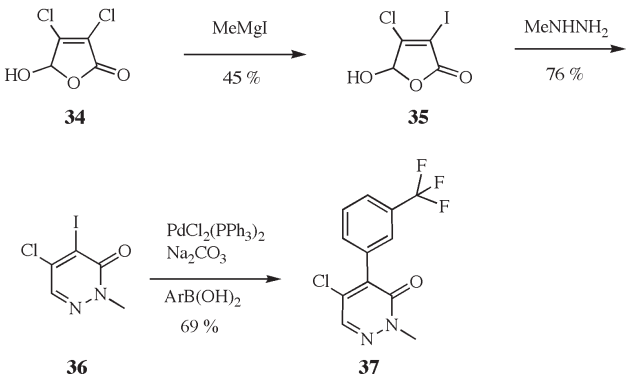
Nonselective Coupling Reaction of 4,5-Dibromopyridazinones

Selectivity of Suzuki Couplings on Dihalopyridazinones.

As we continued to explore the chemistry we investigated the reaction of 4,5-dibromopyridazinones such as **11** with boronic acids. (Scheme 6) As evidenced by the methoxide reactions shown earlier, nucleophilic substitution reactions are fairly selective for the 5-position on these substrates. However, Suzuki couplings with various aryl boronic acids proved quite non-selective. With 1.2 eq of a boronic acid, 2 difficult to separate monoaryl products (**31**) and (**32**) as well as bisaryl product (**33**) and starting material (**11**) were observed. The reactions could readily be pushed completely to the 4,5-bisaryl product (**33**) with 3 eq. of boronic acid. The lack of selectivity limited the potential synthesis of compounds with different carbon bound substituents at the 4- and 5-positions

The problem of how to get different carbon bound substituents on the 4- and 5-positions in a selective manner still remained of interest. [12] We felt that we needed to find a way to get different halogens on each of the two positions. No direct way to accomplish this was readily apparent, but an interesting report from Slovakian workers in the 1970's gave us one potential solution. [13] (Scheme 7) They reported that inexpensive mucochloric acid (**34**) reacted with methyl magnesium iodide in an unusual manner to give a selective halogen exchange reaction resulting in an iodo/chloro mixed mucohalic acid (**35**). After repeating this reaction we examined the reaction of **35** with methylhydrazine, which resulted in ring closure to 5-chloro-4-iodopyridazinone (**36**). Extension of the cyclization with other hydrazines has not yet been investigated, but presumably would also give analogous N-substituted pyridazinones. Suzuki coupling reactions result in products from reaction at the 4-position with this substrate. While disubstitution is not completely suppressed, only one monoaryl product, for example **37**, is obtained resulting from coupling at the 4-position. Palladium catalyzed reactions or nucleophilic displacement reactions may then be used to functionalize the 5-position.

Scheme 7

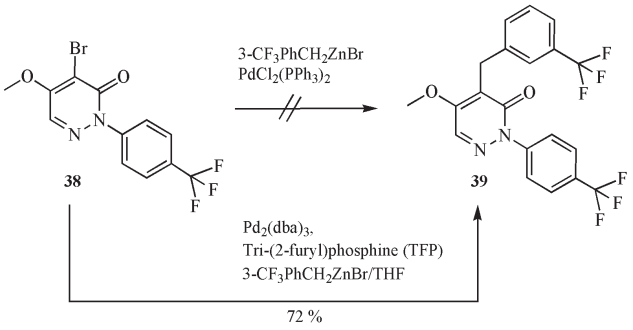


Synthesis and Reactivity of a Mixed Dihalopyridazinone

Pyridazinones in Other Cross Coupling Reactions.

We also investigated a number of other cross coupling reactions. We were very interested in investigating benzylic zinc reagents in Negishi type couplings. (Scheme 8) The zinc reagents were produced from the reaction of zinc activated by Knochel's method with the appropriate benzylic bromide. The coupling reaction was not very efficient using $Pd(PPh_3)_2Cl_2$. However good yields of 4-benzylpyridazinones such as **39** were obtained with N-aryl-4-bromo-5-methoxypyridazinone (**38**) by use of the tri-(2-furyl)phosphine (TFP) ligand. [14] While we did not investigate the use of iodopyridazinones like **36** in Negishi couplings, it is probable that less active catalysts can be successfully used with these substrates.

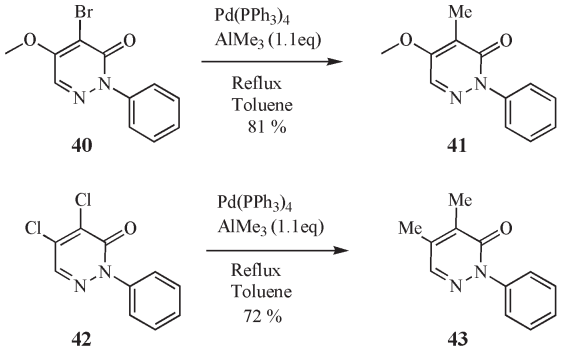
Scheme 8



Negishi Coupling of Benzylic Zinc Reagents

Introduction of a methyl group was successful with trimethylaluminum. (Scheme 9) Reaction of a 4-bromo-5-methoxypyridazinone (**40**) with $Pd(PPh)_4$ as catalyst in refluxing toluene cleanly gave the desired 4-methylpyridazinone (**41**). Under the same conditions attempted selective introduction of one methyl group into the 4,5-dichloropyridazinone (**42**) using 1 equivalent of aluminum reagent proved that trimethylaluminum was capable of transferring at least 2 of its methyl groups to the 4,5-dihalosubstrates to give **43**. Both chloro and bromopyridazinones are good coupling partners for aluminum reagents. While we have not investigated this, based on the work of Benneche and Undheim it seems likely that other trialkylalanes would also transfer alkyl groups to halopyridazinones. [15]

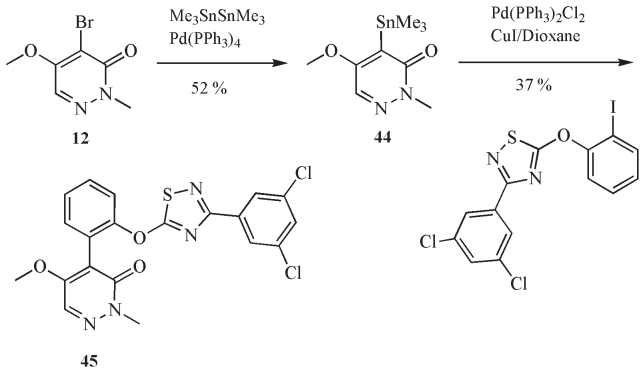
Scheme 9



Cross Coupling with Organoaluminum Reagents

Stille coupling reactions proved very valuable in the strobilurin optimization program. Stille coupling of **12** with hexamethyldistannane gave a tin containing pyridazinone (**44**) suitable for further reaction with aryl iodides to give previously elusive strobilurin analogs. (Scheme 10) This allowed us to prepare strobilurin analogs like **45** from substrates from which boronic acids could not be readily synthesized due to incompatibility with organometallic reagents. For the reactions of the stannylpyridazinone (**44**) with aryl iodides we mainly used Liebeskind's modification of the Stille coupling, which employs CuI as a co-catalyst. [16] Alternatively, TFP was also successfully employed as a ligand for the Stille coupling. While yields were only moderate, this sequence allowed us to easily synthesize and test some hard to obtain strobilurin analogs such as **45**.

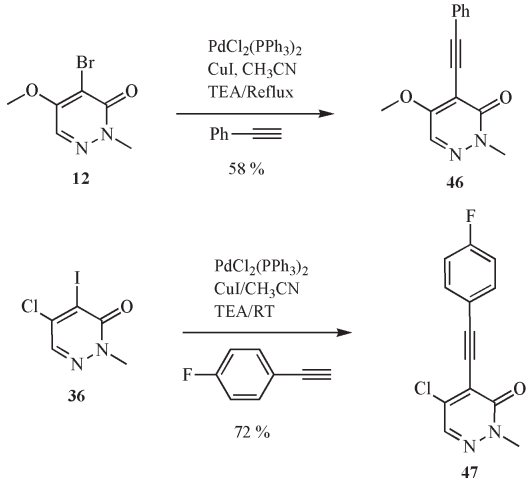
Scheme 10



Stille Coupling Strategy through a Stannylpyridazinone

Introduction of acetylenes into the 4-position of the pyridazinone can also be readily accomplished. (Scheme 11) Sonogashira coupling reactions were

Scheme 11

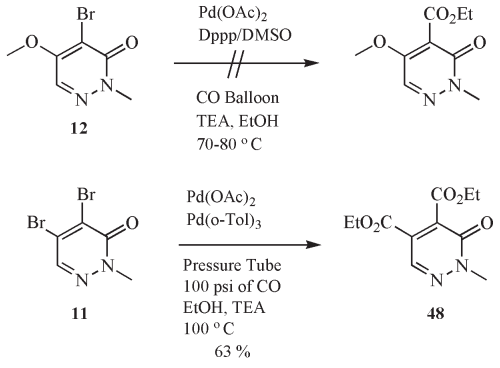


Sonogashira Coupling Reactions

carried out on the bromopyridazinone **12** in refluxing acetonitrile with CuI and $Pd(PPh_3)_2Cl_2$ as catalysts to give, for example, **46** from phenylacetylene. Use of an iodosubstrate (**36**) allowed us to carry out similar reactions at room temperature. The 4-iodo-5-chloropyridazinone (**36**) gave a very selective coupling reaction at the 4-position with acetylenes such as 4-fluorophenylacetylene to give products such as **47**. This chemistry potentially could be used to produce heterocycles by cyclization of **47** with nucleophiles introduced at the 5-position in a subsequent step. [17]

Carbonylation of pyridazinones was also possible under conditions of high pressure. (Scheme 12) The 4-bromo-5-methoxypyridazinone (**12**) did not react with carbon monoxide at atmospheric pressure (balloon) even in the presence of a highly active carbonylation catalyst. [18] However, when a higher pressure of carbon monoxide was

Scheme 12



Carbonylation Chemistry of Pyridazinones

used carbonylation proved much easier. For example, a good yield of the 4,5-diester (**48**) could be obtained from **11** with a less active catalyst and ethanol under 100 psi of carbon monoxide in a pressure tube. [19]

Halogen-Metal Exchange Chemistry of Pyridazinones.

Inhibition of the enzyme p-hydroxyphenylpyruvate oxygenase (HPPO) is the mode of action of compounds like Sulcotrione **49** from Zeneca (Now Syngenta). Other classes of inhibitors include hydroxypyrazoles such as **50** from Nissan. The most potent inhibitors share structural features that include a 2,4-disubstituted or 2,3,4-trisubstituted aryl ketone and an acidic enolic hydrogen. [20] (Figure 3) Comparing the cyclohexanedione and the pyrazolone rings, we envisioned a pyridazinone like **51** might serve the same function. A pyridazinone as the dione component could be imagined to come from demethylation of a 5-methoxypyridazinone which might be synthesized from one of our cross coupling intermediates.

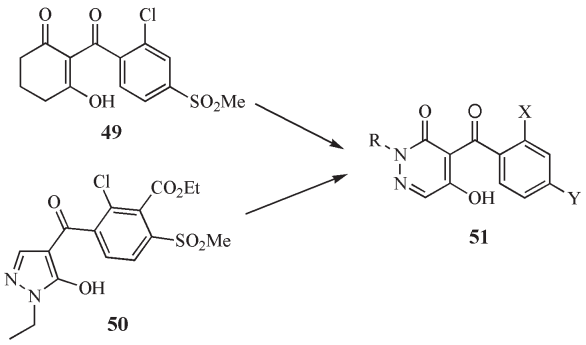
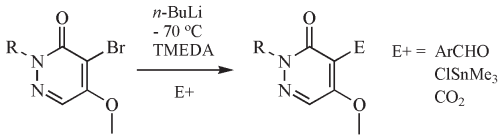


Figure 3. Herbicidal Inhibitors of *p*-Hydroxyphenylpyruvate Dioxygenase (HPPO).

We felt it might be possible to do halogen-metal exchange chemistry on our Suzuki substrates to make 5-benzoylpyridazinones which could serve as precursors to the potential HPPO inhibitors. Attempts at lithiation began with the N-methylpyridazinone (**12**), which was our key intermediate for strobilurin analogs. However, the compound was insoluble in ether and THF below –30 °C and gave rise to capricious results upon lithiation. The addition of TMEDA somewhat mitigated the solubility issues, but did not fully resolve the reproducibility issues. However, when any other pyridazinone with a larger N-substituent (even ethyl) was used solubility was complete even at – 70 °C. Under these conditions halogen-metal exchange was smooth although the lithium reagents were not highly reactive. [21] In a typical reaction, *n*-butyl lithium and TMEDA were added to the substrate and the resulting mixture was stirred at – 70 °C for 10-15 minutes prior to quenching with the electrophile. Importantly, benzaldehydes (the electrophiles needed for the HPPO targets) were good substrates. In addition to benzaldehydes, trimethylstannyl chloride, trimethylsilyl chloride, methyl iodide, deuterium oxide and carbon dioxide gave the expected products while dimethylformamide did not. The products with benzaldehydes were generally not isolated, but converted to ketones by stirring the crude products at room temperature in toluene with excess MnO_2 prior to purification. Some of our results from lithiation chemistry are reported in Table 2.

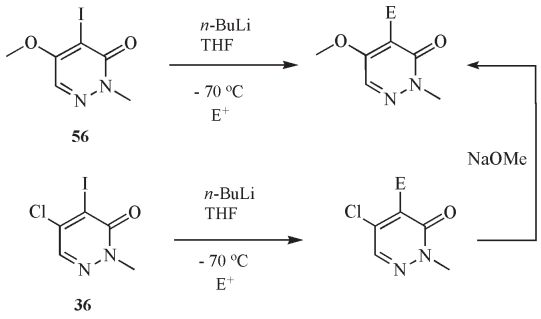


R	E	Reaction Product	Yield (%)
Me	CO-(2,4-DiClPh)	**52**	43[a]
Et	CO-(2,4-DiClPh)	**53**	48[a]
t-Bu	CO-(2,4-DiClPh)	**54**	74[a]
Ph	CO-(4-FPh)	**55**	49[a]
Me	$SnMe_3$	**56**	23
Ph	CO_2H	**57**	28[b]

[a] Yield includes oxidation of crude alcohol with MnO_2. [b] Isolated by esterification with methanol and thionyl chloride.

While the insolubility frustrated our attempts to reproducibly use N-methyl substrates in this chemistry, using iodopyridazinone (**36**) and its methoxide displacement product (**58**) solved this problem. (Scheme 13) We were able to readily carry out halogen-metal exchange on the 4-iodopyridazinones either before or after methoxide displacement. The solubility of both **36** and **58** was very good at low temperatures. In contrast to the straightforward

Scheme 13

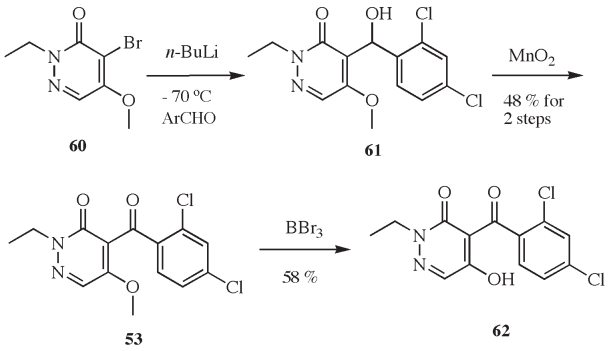


Halogen-Metal Exchange on Iodopyridazinones

halogen-metal exchange reaction of **36**, 4,5-dibromopyridazinones gave complex mixtures of products upon attempted reaction with *n*-butyllithium.

With the reproducible formation of the lithiated pyridazinones in hand we were able to synthesize a variety of 4-benzoylpyridazinones. As outlined in Scheme 14 for the N-ethylpyridazinone (**60**), lithiation of the various pyridazinones followed by quenching with 2,4-dichlorobenzaldehyde and oxidation with MnO_2 gave the masked tricarbonyl (**53**). Deblocking with BBr_3 or TMSI gave the desired targets such as **62**. Extension of this route to other N-substituents and other 2,4-disubstituted benzaldehydes allowed the synthesis of a diverse set of compounds exemplifying structure **51**. Compounds in which the N-substituent was a small alkyl group like **62** proved to be good herbicides. [22] Bleaching symptomology was observed and site of action work confirmed the activity was due to HPPO inhibition at nanomolar concentrations.

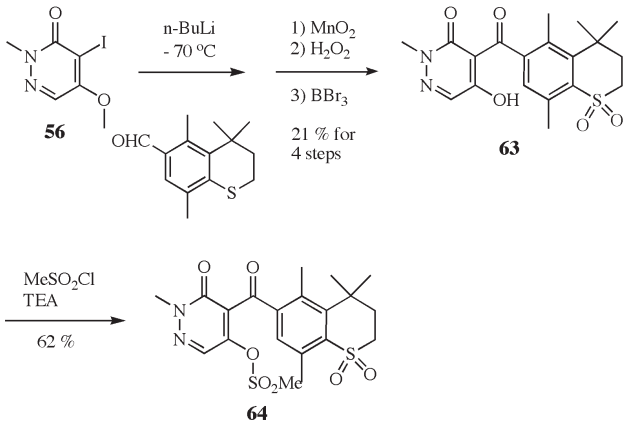
Scheme 14



Synthesis Route to Benzoylpyridazinone Inhibitors of HPPO

An important component of a new generation of HPPO inhibitors is the presence of a bicyclic sulfone. Our first choice for a bicyclic sulfone was a 4,4-dimethylbenzothiopyran since it would be compatible to both lithium reagents as well as to BBr_3. Following the synthetic method outlined in Scheme 15, we were able to make the desired target pyridazinone (**63**) from the pyridazinone (**56**), which showed improved activity as a herbicide. Oxidation of the cyclic sulfide to the sulfone with Oxone™ or hydrogen peroxide could be carried out either prior to or after demethylation. No oxidation of the pyridazinone ring was observed. In addition to the good herbicidal activity, we also observed corn safety with **63**. The physical properties of the pyridazinones could be changed readily by using capping groups. Reaction with thionyl chloride gave the 5-chloro derivative. Capping with sulfonyl chlorides and acid chlorides respectively resulted in highly active

Scheme 15



Synthesis of Bicyclic Sulfone Containing Pyridazinones

molecules such as **64**. Capped compounds like **64** had increased mobility on TLC and higher solubility in organic solvents. Hydrolysis of these "protecting groups" *in vivo* reveals the active herbicide.

The 5-benzoylpyridazinones studied in this work showed good levels of activity in post–emergence testing. Significant safety towards corn was seen in testing of a variety of analogs. The best compounds such as **63** controlled a variety of important weeds at rates as low as 62-125 g/Ha post-emergence in the greenhouse. Compounds with smaller N-substituents such as methyl or ethyl had the highest levels of activity. The structure-activity relationships for substitution in the benzoyl ring followed published trends from the cyclohexanedione literature. [20]

Conclusions.

We have shown that pyridazinones are excellent substrates for metal assisted chemistry. The readily available halogenated pyridazinones are also easily substituted at the 5-position with nucleophiles. In combination, metal assisted reactions and nucleophilic substitution chemistry provide chemists with the opportunity to synthesize a very diverse group of pyridazinones that could not have easily been made earlier. The history of pyridazinones successfully serving as both pharmaceuticals and crop protection agents bodes well for a new generation of pyridazinones, which will be synthesized using emerging synthetic methods in conjunction with established pyridazinone chemistry.

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